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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,188	11/21/2001	Birgit Jordan	DEAV2000A051USNP	9429
5487	7590	08/20/2007		
ANDREA Q. RYAN SANOFI-AVENTIS U.S. LLC 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			EXAMINER CHEN, STACY BROWN	
			ART UNIT 1648	PAPER NUMBER
			NOTIFICATION DATE 08/20/2007	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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**Office Action Summary**

Application No.

09/989,188

Applicant(s)

JORDAN ET AL.

Examiner

Stacy B. Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-46 and 48 is/are pending in the application.
- 4a) Of the above claim(s) 21-46 and 48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-13 and 16-20 is/are rejected.
- 7) ☒ Claim(s) 14 and 15 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 5, 2007 has been entered. Claims 21-46 and 48 are pending and withdrawn from consideration as being drawn to non-elected inventions. Claims 1 and 3-20 are pending and under examination.

### ***Response to Amendment***

2. The following rejections are withdrawn:
- The rejection of claims 8-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment. The claims as amended specify that the zyxin derivative consists of a fusion protein of glutathione S-transferase having the first 142 amino acids of zyxin fused to the C-terminus of said glutathione S-transferase.
  - The rejection of claims 5-7 and 9 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicant's persuasive arguments. Support for the terms, "VASP fragment" and "zyxin

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fragment", were questioned in the rejection, however, Applicant points to paragraph 39 of the specification for support of these terms.

- The rejection of claims 5-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of Applicant's amendment. The genus of VASP fragments and zyxin fragments was questioned in the rejection. Applicant's amendment further defines those fragments as having an EVH1 domain.

### *Claims Summary*

3. The claims are drawn to a process for identifying a chemical compound which modulates an interaction between an EVH1 binding domain (or a protein having said domain) and an EVH1 domain (or a protein having said binding domain). The process comprises the steps of bringing the two proteins in contact in the presence of the candidate compound, incubating the mixture with a primary and secondary labeled antibody that binds to either of the two proteins. Detection of the labeled antibody indicates that the antibody bound said EVH1 domain protein. The process takes place on a solid body, such as a microtiter plate coated with the EVH1 binding domain protein. In particular embodiments, the protein having the EVH1 domain is VASP of a vertebrate, specifically human VASP. The protein having the EVH1 binding domain is zyxin, specifically human zyxin. VASP binds zyxin. Also claimed are polyclonal and monoclonal antibodies in the incubation step of the process. In another embodiment, the antibody label is a radioactive isotope, a fluorescent dye or an enzyme, such as alkaline phosphatase, beta-galactosidase, lanthanide in a europium complex.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-13 and 16-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gertler *et al.* (WO 98/01755, "Gertler"), in view of Reinhard *et al.* (*PNAS USA*, 92:7956-7960, 1995, "Reinhard") and Evangelista *et al.* (US 5,262,299, "Evangelista").

Gertler discloses a screening method for a modulator of a protein (Mammalian Ena, abbreviated "*Mena*") having an EVH1 binding domain that binds to EVH1 proteins such as zyxin and vinculin (abstract). In one embodiment, the modulator is a chemical compound (page 28, lines 28-32). Assays are disclosed suitable for high throughput screening assays designed to identify modulators of *Mena* or Ena-VASP-like (abbreviated *Evl*) expression and/or activity (page 23). In one embodiment, the protein is contacted with a binding partner in the presence of the candidate modulating compound. The protein and its binding pair will either complex or remain separate proteins. If a complex forms, the candidate has no modulation activity on the EVH1 protein or binding domain. If a complex does not form, then the candidate has modulation activity on the EVH1 protein and binding protein (page 23, lines 13 through page 24, line 19). Gertler discloses that secondary antibodies may be used to detect anti-EVH1 antibodies. The assays are conducted on solid phase (page 24, lines 24-29). Also disclosed are monoclonal and polyclonal antibodies that bind to proteins comprising EVH1 domains (page 17,

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lines 16-30). Further, the EVH1 domain protein is a fusion protein with glutathione S-transferase (page 24, lines 24-27). Gertler suggests the use of a solid phase for the assay, however, there is no teaching about a microtiter plate as claimed by Applicant. Gertler suggests the use of labels for the antibodies, however, there is no teaching regarding the types of labels. Specifically, Gertler is silent on alkaline phosphatase or beta-galactosidase, and lanthanide in a europium complex.

However, Reinhard discloses an assay wherein a zyxin family member (p83) was coated to the surface of microtiter wells and human VASP was applied as a ligand (page 7956, column 2, first full paragraph, and page 7958, second column, first paragraph). Reinhard mentions that a human zyxin homologue was discovered (page 7959, first column, first full paragraph).

Reinhard also discloses a double-label immunofluorescence assay wherein monoclonal and polyclonal antibodies labeled with rhodamine and FITC (page 7958, second column, third full paragraph, and Figure 4 caption). Further, Evangelista discloses various labels used for detection assays. The labels include lanthanide chelate (europium complex), alkaline phosphatase and beta-galactosidase (Figures 1-13).

It would have been obvious to incorporate the teachings of Reinhard and Evangelista into the method of Gertler. One would have been motivated to perform the detection assay on a solid support, such as a microtiter plate, in order to test more candidate compounds. One would have had a reasonable expectation of success because Gertler suggests the use of a solid body, and Reinhard performs a similar assay to Applicant's assay with VASP and a zyxin family member. One would have been motivated to use the labels taught by Evangelista because Gertler suggests the use of labels for the antibodies. One would have been motivated to use Evangelista's label

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because Evangelista teaches that the lanthanide label is highly sensitive. As for beta-galactosidase and alkaline phosphate labels, these are common labels in the art of immunoassay, evidenced by Evangelista's Figures detailing several of the well-known labels in the art. Regarding the limitation of claim 13, wherein the monoclonal antibody is synthesized using hybridoma cells, Gertler's monoclonal antibodies anticipate this limitation. Monoclonal antibodies are only ever produced from hybridoma cells to date. Regarding the use of human VASP and zyxin in the immunoassay, one would have been motivated to use human proteins in order to discover chemical compounds appropriate for human administration should any be found effective and safe. Therefore, the invention as a whole would have been *prima facie* obvious at the time of the invention.

5. Applicant's arguments have been carefully considered but fail to persuade. Applicant's arguments are primarily directed to the following:

- Applicant maintains its position that the Office has mischaracterized the teachings of Gertler. Specifically, Applicant asserts that Gertler makes no apparent distinction between an EVH1 domain and an EVH1 binding domain. Applicant argues that there is no teaching or suggestion as to which domains or fragments of the molecules participate in the binding.
- In response to Applicant's arguments, Gertler's assay and the reagents used in the assay meet the claim limitations. Gertler may not have appreciated the full mechanism of binding, or fully characterized the specific portions of the proteins involved in the interaction of binding, however, the binding that takes place in

Gertler's assay is expected to be the same binding that occurs in Applicant's assay because the reagents are the same. The proteins that bind are the same, and thus the interaction between the two is expected to be the same as that elucidated by Applicant.

- Applicant argues that Gertler's assay is directed to modulation of Mena activity such as by using competitive proteins or triplex forming oligonucleotides to study microfilament assembly. Applicant asserts that the assay is directed to a different problem than addressed by the instant invention.
  - In response to Applicant's arguments, the instant claims identify a compound that modulates an interaction between EVH1 binding domain and a protein having an EVH1 domain. The instant claims offer no further specifics as to the purpose of the assay such that the assay of Gertler does not read on the claimed invention. That Gertler studies microfilament assembly by modulating Mena activity does not disqualify the teachings of Gertler relating to a screening method for a modulator of a protein (Mammalian Ena, abbreviated "*Mena*") having an EVH1 binding domain that binds to EVH1 proteins such as zyxin and vinculin (abstract). Page 8, lines 26-38 of Gertler, disclose methods suitable for high throughput screening assays designed to identify modulators of *Mena* or Ena-VASP-like (abbreviated *Evl*) expression and/or activity (see page 28, lines 28-32 and also page 23).



***Conclusion***

6. No claim is allowed. Claims 14 and 15 are objected to for depending from rejected claims.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 8-13-2007  
Primary Examiner, TC1600